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Michael R. Ward
Morrison & Foerster LLP
425 Market Street
San Francisco, CA 94105-2842

| EXAMINER | |
|---|---|
| SWITZER, JULIET CAROLINE | |
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| 1634 | |

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/091,841 | CHO ET AL. | |
| | Examiner | Art Unit | |
| | Juliet C. Switzer | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *29-49,65-70 and 73-94* is/are pending in the application.

4a) Of the above claim(s) *47-49* is/are withdrawn from consideration.

5)☒ Claim(s) *32,68,75 and 78* is/are allowed.

6)☒ Claim(s) *29,31,33-46,65,67,69,70,74,77 and 79-94* is/are rejected.

7)☒ Claim(s) *30,36-40,43-45,66,69,70,73,76,79-90 and 92-94* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 12/29/03. Claims 29-32, 35-38, 40, 43-44, 65-70, and 76-90 have been amended, claims 1-28, 50-54, and 71-72 have been cancelled. Claims 29-49, 65-70, and 73-94 are pending, claims 47-49 are withdrawn from prosecution as they are non-elected. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

### *Election/Restrictions*

2. Applicant's election with traverse of Group I in the paper filed 12/29/03 is acknowledged. The traversal is on the ground(s) that the polypeptides of group II are not distinct from the polynucleotides of group I because the polypeptides are expressed from the nucleic acids, and there is no additional search burden to search both the nucleic acids and the polypeptides. This is not found persuasive because Although the polynucleotides and polypeptides are related as the claimed polynucleotide is asserted to encode the claimed polypeptide, they are distinct inventions because they are physically and functionally distinct chemical entities, and the protein product can be made by another and materially different process, such as by synthetic peptide synthesis or purification from the natural source. Further, the DNA may be used for processes other than the production of the protein such as in hybridization detection assays. The search of the proteins is not coextensive with that of the nucleic acids, as is evidenced by the separate

classification of the products, and further the searches of the non-patent literature require the search of separate databases, both in text searches and in sequence searches.

The requirement is still deemed proper and is therefore made FINAL.

3. This application contains claims 47-49 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Specification*

4. The objections to the specification are withdrawn in view of applicant's amendments.

### *Claim Objections*

5. Claims 36, 37, 38, 39, 40, 43, 44, 45, 69, 70, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 92, 93, and 94 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims do not properly limit the parent claims from which they depend, because they do not require all of the limitations of the parent claim. This is exemplified by the fact that claim 30 is not rejected in view of the prior art herein, but claim 79 which depends from claim 30 is rejected in view of the prior art.

### *Claim Rejections - 35 USC § 112*

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 36, 37, 38, 39, 40, 43, 44, 45, 69, 70, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 92, 93, and 94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite over the recitation "the recombinant nucleic selected from" or "the isolated nucleic acid selected from" (as appropriate) because this phrase lacks proper antecedent basis in the claims as the claims do not previously refer to a selected recombinant or isolated nucleic acid, and thus it is not clear which nucleic acid is "the" nucleic acid selected from the group.

Furthermore, claims 37, 38, 39, 40, 44, 45, 70, 82, 83, 84, 85, 86, 87, 88, 89, 90, 93, and 94 are indefinite because it is not clear from the recitation of these claims which sequence is intended to be "operably linked to transcriptional regulatory sequences active..." For example, turning to claim 90, it is not clear if the claim means to set forth that each of the three recited nucleic acids are operably linked or if the claim means to set forth that only a nucleic acid encoding SEQ ID NO: 25 is operably linked to transcriptional regulatory sequences.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 31, 33-46, 65, 67, 69-70, 74, 77, 80, 83, 86, 89, and 91-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are drawn to recombinant nucleic acids encoding an NADPH-thioredoxin reductase protein (NTR protein) and compositions comprising these nucleic acids. Claims 29 and 65 are broadly drawn to include recombinant and isolated nucleic acids encoding an NTR protein which hybridizes under high stringency conditions to SEQ ID NO: 10. All of the rejected claims recite that the protein has "NTR biological activity." However, the specification does not provide a limiting definition for "NTR biological activity," and as such, any activity which is attributable to an NTR protein, the ability to raise antibodies, to be a substrate for a protease, etc. is encompassed within this broad functional language. The specification, at page 15 teaches a "preferable" definition of the phrase "NTR biological activity" but this preferable limitation cannot be read into the claims due to the use of the non-limiting language "preferable." While the claims recite that the nucleic acid encodes an "NTR protein" and have "NTR biological activity" it is not clear from the language of these claims what functionality the encoded proteins must have. Claims 31 and 67 are broadly drawn to include nucleic acids encoding an NTR protein, where in said nucleic acids comprise nucleic acids with 95% sequence identity to SEQ ID NO: 10. Once again, these claims do not include clear functional language to limit or describe the protein encoded by the claimed polynucleotide. Further, even in light of such functional language, the specification does not provide guidance as to how to arrive at sequences which have only 95% identity to SEQ ID NO: 10 yet still retain the functionality of instant SEQ ID NO: 10. All of the other rejected claims depend from these independent claims.

Claims 36, 37, 38, 39, 40, 41, 43, 44, 45, 46, 69, 70, 80, 83, 86, 89, 92, 93, and 94 additionally recite transgenic plants, seeds, and methods using said products which recite polynucleotides that hybridize to SEQ ID NO: 26 and SEQ ID NO: 27 or that have a 95% identity to SEQ ID NO: 26 and SEQ ID NO: 27, wherein the recited nucleic acids encode a "NTR protein having NTR biological activity."

The instant specification only describes three nucleic acids which encode NTR proteins, that is a sequence from barley, instant SEQ ID NO: 10 as well as sequences from E. coli and A. thaliana (SEQ ID NO: 25 and 26, respectively).

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of a polynucleotides which encode NTR proteins, wherein the polynucleotides comprise instant SEQ ID NO: 10, 25, and 26. The subject matter which is claimed is described above.

First, a determination of the level of predictability in the art must be made in that whether the level of skill in the art leads to a predictability of structure; and/or whether teachings in the application or prior art lead to a predictability of structure. The claims are directed nucleic acids encoding an NTR protein, and encompass such nucleic acids from any plant species, as well as any variants which may that have as little as to 95% identity to SEQ ID NO: 10, SEQ ID NO: 25, and SEQ ID NO: 26. The specification only describes only three nucleic acids encoding a NTR proteins and fails to teach or describe any other NTR proteins encoding polynucleotides. With regard to SEQ ID NO: 10, SEQ ID NO: 25, and SEQ ID NO: 26, the specification does not teach

any variants or homologues of SEQ ID NO: 10, SEQ ID NO: 25, or SEQ ID NO: 26 that also encode NTR proteins (active or inactive proteins). Therefore, there is a lack of guidance or teaching regarding structure and function because there are minimal examples provided in the specification and because there is no guidance found in the with regard to all of the variation of sequence encompassed within the instant claims.

Next in making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, each claimed species and genus must be evaluated to determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed. With this regard, the instant application fails to provide a written description of the species or the genus which are encompassed by the instant claims, beyond the nucleic acid disclosed as SEQ ID NO: 10, 25, and 26. The specification does not provide any disclosure as to how the instant encoded polypeptides can be modified and still retain the disclosed biological activity. The claims also fail to recite other relevant identifying characteristics (physical and/or chemical and/or functional characteristics coupled with a known or disclosed correlation between function and structure) sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only the SEQ ID NO: 10, 25 and 26 are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of any NTR protein encoding nucleic acids which comprises sequences that will hybridize under highly stringent conditions to SEQ ID NO: 10, 25, or 26 or with as little as 95% homology to SEQ ID NO: 10, 25, or 26.

9. Claims 29, 31, 33-46, 65, 67, 69-70, 74, 77, 80, 83, 86, 89, and 91-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids, constructs, compositions, and methods which comprise or utilize instant SEQ ID NO: 10, 25 or 26 (in their entirety), as well as a nucleic acid encoding instant SEQ ID NO: 9, 24 or 25, does not reasonably provide enablement for any nucleic acid which hybridizes under high stringency conditions to these nucleic acids, or any nucleic acid that has 95% homology to these nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

**Nature of the invention, Breadth of the Claims**

These claims are drawn to recombinant nucleic acids encoding an NADPH-thioredoxin reductase protein (NTR protein) and compositions comprising these nucleic acids. Claims 29 and 65 are broadly drawn to include recombinant and isolated nucleic acids encoding an NTR protein

which hybridizes under high stringency conditions to SEQ ID NO: 10. All of the rejected claims recite that the protein has "NTR biological activity." However, the specification does not provide a limiting definition for "NTR biological activity," and as such, any activity which is attributable to an NTR protein, the ability to raise antibodies, to be a substrate for a protease, etc. is encompassed within this broad functional language. The specification, at page 15 teaches a "preferable" definition of the phrase "NTR biological activity" but this preferable limitation cannot be read into the claims due to the use of the non-limiting language "preferable." While the claims recite that the nucleic acid encodes an "NTR protein" and have "NTR biological activity" it is not clear from the language of these claims what functionality the encoded proteins must have. Claims 31 and 67 are broadly drawn to include nucleic acids encoding an NTR protein, where in said nucleic acids comprise nucleic acids with 95% sequence identity to SEQ ID NO: 10. Once again, these claims do not include clear functional language to limit or describe the protein encoded by the claimed polynucleotide. Further, even in light of such functional language, the specification does not provide guidance as to how to arrive at sequences which have only 95% identity to SEQ ID NO: 10 yet still retain the functionality of instant SEQ ID NO: 10. All of the other rejected claims depend from these independent claims.

Claims 36, 37, 38, 39, 40, 41, 43, 44, 45, 46, 69, 70, 80, 83, 86, 89, 92, 93, and 94 additionally recite transgenic plants, seeds, and methods using said products which recite polynucleotides that hybridize to SEQ ID NO: 26 and SEQ ID NO: 27 or that have a 95% identity to SEQ ID NO: 26 and SEQ ID NO: 27, wherein the recited nucleic acids encode a "NTR protein having NTR biological activity."

**State of the Art, Level of Unpredictability**

The prior art, as taught by the specification teaches the nucleic acid sequence encoding an NTR protein from both E. coli and from Arabidopsis (SEQ ID NO: 25 and 26 herein). Instant SEQ ID NO: 10 is a nucleic acid sequence encoding an NTR protein from barley. The prior art does not provide any guidance as to how to modify these nucleic acids yet result in nucleic acids which encodes NTR proteins that retain their oxidoreductase activity.

The level of unpredictability with regard to such modifications is quite high. Enzyme function and activity is intrinsically related to the structure of the enzyme, and even single amino acid changes can alter the functionality of an enzyme. This point is exemplified repeatedly in the prior art, with regard to reductase enzymes in particular. For example, Gilberger *et al.* (The Journal of Biological Chemistry, Vol. 272, No. 47, pages 29584-29589, 1997) teach that changes in the active site of a thioredoxin reductase from Plasmodium either results in total loss of activity or significant loss of activity, depending on the exchanged amino acid (abstract and throughout). Nagai *et al.* (Blood, Vol. 81, No. 3, p. 808-814, 1993) teach a single amino acid change in the NADH cytochrome b5 reductase caused a significant reduction in enzyme activity which explains a patient's hereditary methemoglobinemia. In a third example, Bullerjahn *et al.* (the Journal of Biological Chemistry, Vol. 267, No. 2, p. 864-870, 1992) teach tha tdeletion mutations of a dihydrofolate reductase lost activity and were more unstable than the wild type. Thus, these exemplify, that modifications to encoded enzymes are highly unpredictable and often result in loss of activity.

**Working Examples and Direction Provided**

The specification does not provide any particular guidance or examples of nucleic acids that are modified with regard to the disclosed sequences, yet the instant claims encompass nucleic acids that encode a widely variant polypeptides considering the changes allowed within the language of the rejected claims.

**Conclusion**

Thus, in light of the breadth of the claims, the high level of unpredictability in the prior art, the lack of guidance provided in the prior art or the instant specification, and the lack of working examples other than the sequences given in the instant specification, it is concluded that it would require undue experimentation to practice the invention commensurate in scope with the instant claims.

***Claim Rejections - 35 USC § 102***

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 29, 33-35, 41-42, 46, 65, and 91 are rejected under 35 U.S.C. 102(e) as being anticipated by Lalgudi *et al.* (US 6476212).

Lalgudi *et al.* teach an isolated nucleic acid which has 89.8% local similarity with nucleotides 1-226 of instant SEQ ID NO: 10. Specifically, nucleotides 29-250 of SEQ ID NO:

3512 as taught by Lalgudi *et al.* is 89.8% identical to nucleotides 1-226 of instant SEQ ID NO: 10. An alignment of the two sequences is as follows, the top sequence being SEQ ID NO: 10 and the bottom sequence being SEQ ID NO: 3512 from Lalgudi *et al.*

```
Qy          1 ATGGAGGGATCCGCCGCGGCGCCGCTCCGCACGCGCGTGTGCATCATCGGCAGCGGCCCG 60
              || ||||||||||||||| || |||||||||| |||| | |||||||||| ||||| ||
Db         29 ATNGAGGGATCCGCCGCCGCTCCGCTCCGCANGCGCATCTGCATCATCGGGAGCGGTCCC 88

Qy         61 GCCGCGCACACGGCGGCCATCTACGCGGCCCGCGCGGAGCTCAAGCCCGTGCTCTTCGAG 120
              || |||||||||| ||||||||||||||||||||||| ||||||| ||||||||||||
Db         89 GCTGCGCACACGGCAGCCATCTACGCGGCCCGCGCGGAG-TCAAGCCTGTGCTCTTCGAG 147

Qy        121 GGCTGGATGGCCAACGACATCGCCGCGGGGGGCCAGCTCACCACCACCACCGACGTCGAG 180
              |||||  |||||||||||||||||||||| || ||||||||||||||||||||||||||
Db        148 GGCTG--TGGCCAACGACATCGCCGCGGGCGGGCAGCTCACCACCACCACCGACGTCGAG 205

Qy        181 AACTTCCCCCGGATTCCCCACCGGCATCATGGGCATCGACCTCATGG 226
              || ||||| || ||||||| |||||||||||||  ||||||||||
Db        206 AA-TTCCCGGGCTTCCCCAACGGCATCATGGGCGCCGACCTCATGG 250
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With regard to claims 29 and 65, Lalgudi *et al.* teach a recombinant nucleic acid encoding an NTR protein comprising a nucleic acid that hybridizes under high stringency conditions to instant SEQ ID NO: 10. Considering the high level of homology between the nucleotide sequence taught by Lalgudi *et al.* and the portion of instant SEQ ID NO: 10, the sequence taught by Lalgudi *et al.* would be expected to hybridize under high stringency conditions to instant SEQ ID NO: 10. The nucleic acid encoded by the SEQ ID NO: 3512 taught by Lalgudi *et al.* is considered to be an "NTR protein" because it encodes at least a portion of an NTR protein, and is considered to have "NTR biological activity" because it would be cleavable by a protease or it would be useful for raising antibodies, both of which are "NTR biological activities."

With regard to claim 33, Lalgudi *et al.* teach a host cell comprising the nucleic acid (Col. 14, line 64).

With regard to claim 34, Lalgudi *et al.* teach an expression vector containing the nucleic acid operably linked to a transcriptional regulatory sequence (Col. 32, lines 63-67).

With regard to claim 35 Lalgudi *et al.* teach a host cell comprising an expression vector comprising the nucleic acid operably linked to a transcriptional regulatory sequence active in said host cell (Col. 33, lines 5-64).

With regard to claims 41, and 42, Lalgudi *et al.* teach a method of expressing an NTR protein comprising culturing the host cells of their invention under conditions suitable for expression of said protein (Col. 14, line 64-Col. 15, line 2).

With regard to claims 46 and 91, Lalgudi *et al.* teach recovering said protein (Col. 15, lines 1-2).

Therefore, the teachings provided by Lalgudi *et al.* meet the limitations of the instantly rejected claims.

***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 36, 37, 38, 39, 40, 43, 44, 45, 69, 70, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 92, 93, and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacquot *et al.* in view of Shi *et al.* (Plant Molecular Biology 32:653-662, 1996).

Jacquot *et al.* teach the nucleic acid encoding Arabidopsis thaliana NADPH-dependent thioredoxin reductase (NTR). Jacquot *et al.* teach that the isolated nucleic acid was disclosed as

EMBL accession number Z23109 (p. 1358, Col. 1), which is included in this office action for applicant's convenience. The coding sequence of nucleic acid taught by Jacquot *et al.* is identical to the A. thaliana sequence provided in instant figure 5A, and encodes a polypeptide identical to the A. thaliana amino acid sequence provided in instant figure 4. Jacquot *et al.* refer to this nucleotide sequence throughout their paper as ATTHIREDB). The nucleic acid taught by Jacquot *et al.* comprises instant SEQ ID NO: 26 and encodes SEQ ID NO: 24. Such a nucleic acid would hybridize under high stringency conditions to SEQ ID NO: 26 and has at least 95% identity to SEQ ID NO: 26.

Jacquot *et al.* teach a host cell comprising the nucleic acid (E. coli host cells, p. 1360-1361).

Jacquot *et al.* teach an expression vector containing the nucleic acid operably linked to a transcriptional regulatory sequence (p. 1361, Col. 1).

Jacquot *et al.* teach a host cell comprising an expression vector comprising the nucleic acid operably linked to a transcriptional regulatory sequence active in said host cell (p. 1361, Col. 1).

Jacquot *et al.* teach a method of expressing an NTR protein comprising culturing the host cells of their invention under conditions suitable for expression of said protein (p. 1361, Col. 1-2).

Jacquot *et al.* teach recovering said protein (p. 1361, Col. 1).

Jaquot *et al.* do not teach transgenic plants which comprise the NTR encoding nucleic acids or constructs.

Shi *et al.* teach transgenic plants comprising recombinant nucleic acids encoding thioredoxins, as well as the seeds of these transgenic plants ("mature plants with pods") (p. 658). methods for transforming plants with thioredoxins (p. 654). Further, Shi *et al.* teach methods for expressing a thioredoxin protein which comprise culturing a plant comprising the recombinant nucleic acid under conditions suitable for expression of the thioredoxin (p. 654, 656), as well as methods of expressing a thioredoxin which comprise culturing transgenic seeds (p. 658). Shi *et al.* teach methods for recovering the expressed protein (p. 657-658).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have expressed the nucleic acid taught by Jaquot *et al.* in tobacco plants as taught by Shi *et al.* The ordinary practitioner would have been motivated to have produced transgenic plants expressing the NTR protein taught by Jaquot *et al.* in order to have provided an alternative method to for the production of the NTR protein, since Shi *et al.* teach methods for producing an enzyme in transgenic plants and then recovering it using the FLAG epitope. Alternatively, the ordinary practitioner would have been motivated to produce plants expressing the NTR protein in order study the functioning of the NTR in plants since Jaquot *et al.* teach the NTR protein in plants has not been well characterized, as it had only been previously isolated from E. coli (p. 1358).

**Response to Remarks**

The written description rejection is reiterated for each of the claims that retain either hybridization or homology language. The rejection is modified to address the amended claims.

With respect to highly stringent conditions, applicant argues that the specification clearly conveys to one of skill in the art that the inventor had possession of the claimed invention. Applicant refers to Example 9 of the Synopsis of Application of the Written Description guidelines to support this position. However, there are significant differences between the example in the synopsis and the instant application. First, as discussed in the rejection, the "functional language" provided in the instant claims is not adequate to imply a predictable structure for the claimed nucleic acids. Due to the open language used in the specification to define the terms used in the claims, the interpretation of the recited function is broad, including the reduction of thioredoxin but also other possible NTR biological activities, as discussed in the rejections of record. Thus, the claims herein are not limited to nucleic acids that encode a protein with a specific activity. Further, in the example the specification includes an example where the complement of their sequence was used under highly stringent conditions for the isolation of cDNAs that encode proteins with the activities that are recited in the claims, and thus the specification demonstrates that within the genus of nucleic acids that hybridize under highly stringent conditions to their sequence, at least some exist that are within the claimed genus. Further, the example defines highly stringent conditions, while the instant specification appears merely to rely on the "skill in the art" to define this critical factor within these claims (p. 20-21 of the instant specification). This broad definition of "highly stringent" allows for a large degree of variability for one interpreting the claim to determine what in fact are "highly stringent" and thus it is not possible to conclude that the genus encompassed within the rejected claims is properly described. With regard to the claims which recite homology language, applicant's

arguments rely on those set forth for the hybridization type claims. Thus, for the same reasons, this rejection is maintained.

Applicants argue that the scope of the claim is not broad, citing the written description guidelines to support the position that a person of skill in the art would not expect substantial variation among species encompassed within the claims. However, as discussed in the written description rejection, the instant fact pattern differs significantly from that in the cited example, thus, the scope of the claim is broader than applicant implies.

Further, though the skill in the art was high, the level of unpredictability is also quite high, as is discussed in the enablement rejection. It is highly unpredictable how the sequences recited in the claims could be modified yet still retain any activity that is the same as that provided in the claims or the specification. No guidance is provided in this regard. Furthermore, as previously noted, the language used to define the activity which applicant asserts could be routinely screened for is broad and non-limiting, thus it is unpredictable how to screen for such activity, or what activities are included within the claim. Though one could perform hybridizations to isolate sequences or one could determine what is within 95% homology one could not predict how any changes from the sequences recited in the specification would alter the encoded polypeptides. Applicant provides discussion about claims to antibodies which are "well established" to be allowable, however this discussion is not germane to the instant application because the instant claims are not to antibodies. Each application must be examined on its own merits.

In the instant case, in a consideration of all of the factors for determining scope of enablement, particularly the breadth of the claims, the high level of unpredictability, the single

working example, and the lack of guidance as to how to modify the disclosed nucleic acids, the rejection of record is maintained.

Applicant traverses the rejection under Lalgudi *et al.*, providing a declaration by Bob Buchanan, inventor in the instant application to support the position that the nucleic acid taught by Lalgudi *et al.* would not have the requisite NTR biological function. However, as discussed throughout this office action, the claims are not limited to the NADPH reductase function referred to by applicant and the declaration because of the broad nature of the defintion of "NTR biological function" provided in the specification. Therefore, as discussed in the rejection, the rejection is maintained because the nucleic acid would share some "NTR biological function" in common with the disclosed nucleic acids. The rejection is maintained.

Applicant asserts that a prima facie case for obviousness has not been established in the rejection of the claims in under Jacquot *et al.* in view of Shi *et al.* (p. 20 of response). Applicant quotes a short portion of MPEP 2143.01 which states that the prior art must suggest the desirability of the claimed invention. Applicant quotes a heading from the MPEP. The text which immediately follows the heading reads

> "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457- 8 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. Al-Site Corp. v. VSI Int 'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

suggestion, or motivation to do **so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art** (bold emphasis added).

In the instant case, two separate motivations to combine the references are provided which ar provided implicitly by the references themselves. Jaquot *et al.* teach the NTR protein in plants has not been well characterized, as it had only been previously isolated from E. coli, and thus it is implicit within this disclosure that it would be desirable to further study the enzyme, and Shi *et al.* demostrate methods for studying enzymes within transgenic plant systems. Further, with regard to an alternative method to produce the enzyme, the production of a plant enzyme within a plant, as opposed to E. coli, would have been desirable because of the difference in post translational modification of the enzyme within a plant system versus a bacterial system. Thus, contrary to applicant's assertions, adequate motivation is provided to combine the references, and the rejection is maintained.

***Conclusion***

14. An isolated nucleic acid comprising instant SEQ ID NO: 10 is free of the prior art, as is an isolated nucleic acid encoding instant SEQ ID NO: 9.

15. Claims 32, 68, 75, and 78 are allowed.

16. Claims 30, 66, 73, and 76 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Juliet C Switzer
Examiner
Art Unit 1634

February 3, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER